Comparative Effectiveness Review Disposition of Comments Report

Research Review Title: *Medical Therapies for Children With Autism Spectrum Disorder —An Update*

Draft review available for public comment from September 6, 2016 to October 3, 2016.

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Comments to Research Review

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The tables below include the responses by the authors of the review to each comment that was submitted for this draft review. The responses to comments in this disposition report are those of the authors, who are responsible for its contents, and do not necessarily represent the views of the Agency for Healthcare Research and Quality.

Commenter and Affiliation	Report Section	Comment	Response
TEP Reviewer #1	Clarity and Usability	Overall the report was well structured and organized. The main points are clearly presented and conclusions are relevant. Given the diverse audience who would be reading the report, and the wide range in their skill, knowledge base, familiarity with systematic and/or CER, the report might benefit from simplifying and/or clarifying the abstract.	We have revised the abstract to improve clarity.
Peer Reviewer #2	Clarity and Usability	Basically all very clear (but see comments above).	Thank you for your comments.
TEP Reviewer #3	Clarity and Usability	The report is well organized; I was able to quickly find areas of interest to me, and then to go back and review the entire manuscript in a more chronologic format. the reader will be able to find specific areas of interest quickly, as well as broader summaries and the details of the appendices. Conclusions are relevant to practice decisions, and have implicatons for policy / funding of future research. A problem with reviews of this type is that the positive aspects of the review (what does work, what doesnt) is often overlooked by excessive focus on weaknesses and future/ additional research needs. The tone overall is good, not overly negative, such that a clinician can find suggestions / support for treatments while gaining / reinforcing those weak points that need to be considered.	Thank you for your comments.
TEP Reviewer #4	Clarity and Usability	"...may be used to treat symptoms of ASD" This line is easily taken out of context, and could be interpreted as an endorsement of this treatment approach.	We changed this to read "have been used."
TEP Reviewer #5	Clarity and Usability	I think that the conclusions are clearly relevant to policy and practice decisions.	Thank you for your comments.
Peer Reviewer #1	Clarity and Usability	Overall, this is a very well structured and well organized report. It is succinct and concise and the main findings, and caveats about existing research, are clearly presented. My main reservation, as indicated above, is that the clinical implications of the findings (i.e. that there is little or no evidence to support the use of medical treatments with this age group) should be given greater emphasis.	Thank you for your comments. We have revised the conclusions section to strengthen the "bottom-line" messages.
TEP Reviewer #1	Clarity and Usability	The medical abstract would befit from reiteration of why 2-12 years selected; clarification on treatments used for children with ASD, and a sentence (such as a shorter version of that found in the introduction "Individual goals for treatment vary for different children and may include combinations of behavioral therapies, educational therapies, medical and related therapies, approaches targeting sensory issues, and allied health therapies; parents may also pursue complementary and alternative medicine therapies.")	We have added information on the age range to the Scope of Review section of the main report. Word limitations prohibit our adding extensive methodologic information to the abstract.

TEP Reviewer #5	Clarity and Usability	I think that the report is well-structured and clear with the exception of ADHD medications, as I noted above.	We have restructured the report to include a section on ADHD medications, which includes MPH, atomoxetine, and guanfacine.
TEP Reviewer #1	General Comments	This (combined) report is clinically meaningful, and addresses an extremely important area for the audience: consumers (children with ASD and their parents) and providers. It serves as a valuable resource as a compendium/collection of research evidence for multiple treatments in use. The target population is well described and defined - however, it would be helpful to the reader if the authors would reiterate explicitly the rationale for limiting the age range to 2-12 years in the early parts of the report.	Thank you for your comments. We have added more detail about our restriction to children ages 2-12 in the Scope of Review section (e.g., focus on children with confirmed diagnoses).
TEP Reviewer #1	General Comments	Key questions are appropriate and explicitly stated. The introduction to the report, describing the intent and purpose of the systematic reviews are helpful (pages ii – iv, depending on which report).	Thank you for your comments.
TEP Reviewer #2	General Comments	The report is clinically meaningful and the questions explicitly stated. the key questions were fair and similar to those one would want to know about any therapy.	Thank you for your comments.
Peer Reviewer #2	General Comments	Both reviews are generally well-written and clear. I only have a few small points that should be addressed.	Thank you for your comments.
Peer Reviewer #2	General Comments	One point that was unclear to me was what time frame the authors considered to be "long-term": ≥ 6 months; > 6 months; ≥ 12 months; or > 12 months? This seemed to be inconsistent between different sections. KQs define short term as ≤ 6 months and longer-term as >6 months, but the abstract describes short term as < 12 months.	We have clarified the time frame to reflect ≤ 6 months as short term and greater than 6 months as long term.
Peer Reviewer #2	General Comments	Lists of excluded studies were mostly but not completely in alphabetical order. A few references at the beginning did not follow that order (perhaps they were added later?).	The excluded studies appendix is organized by year and then alphabetically.
Public Reviewer #2 (Tristram Smith)	General Comments	Lengthy and somewhat confusing as the major topic areas were presented with conclusions and then further in the document, there's more description of the studies presented with the same conclusions which made it all seem redundant.	We have attempted to reduce redundancy throughout the reports but note that the medical report includes an executive summary, which includes a more concise presentation of information in the full report. The reports also include "key points" sections to present key messages for each section.
TEP Reviewer #4	General Comments	This report will be very valuable to the autism patient community, as they seek information to help guide their treatment decisions, and to the autism research and research funding community, as they evaluate the gaps in current knowledge and the most important directions that research should pursue.	Thank you for your comments.
TEP Reviewer #4	General Comments	Figure ES-1 (repeated as Fig 1, on p. 31? and p. 122?) requires review and revision. It indicates a KQ7, but there is no such KQ. I am not sure that the other KQ symbols are correctly located on the figure.	We have revised the figure to correct this oversight.

TEP Reviewer #5	General Comments	Note: the report is generally well-written with few typos. In the context of being asked to perform an expert review, I have not dwelled on typos or minor errors but instead focus on more substantial issues.	We hope that we have caught and corrected any typos. We appreciate the reviewer's thoughtful comments on the content of the report.
Peer Reviewer #1	General Comments	This is a well written and very helpful report. I am not a physician and so my knowledge of the pharmacological literature in this area is not extensive, Therefore I cannot really judge how comprehensive the literature review of medications is. However, there were certainly no obvious references that were missing. The report is of clinical relevance as many studies have highlighted the high rates of medication use in this patient group- often without attention to adverse effects or long term consequences. The limited data on most of the medications discussed, and the potential for possible harm associated with most of the medications reviewed is clearly of high clinical importance.	Thank you for your comments.
Peer Reviewer #1	General Comments	The target population for the study is well defined and key questions appropriate and explicitly stated.	Thank you for your comments.
TEP Reviewer #3	General Comments	The report is clinically meaningful and thorough. Medical treatment of autism spectrum disorder is an important part of overall management, and frequently medical treatment alone is used when there is poor access to non-medical therapies. The studies identified are appropriate and the analysis of the studies follows recommended guidelines for grading strength of evidence. A strength of the paper is its inclusion of studies of "outcomes of interest" and not restricted to only studies of treatment of core symptoms of ASD. The review / inclusion of sensory related therapies is also important as many of these are used with little consensus regarding their benefit.	Thank you for your comments.
TEP Reviewer #4	General Comments	As the report itself points out, the combination of medical with behavioral/parent training is potentially a very important direction for future research. While the full report does review the RUPP studies that examined the combined use of risperidone and parent training, there is no mention of this in the Executive Summary. I strongly recommend that this be mentioned, even though little data are currently available, since many other approaches with little data are mentioned there.	We have added text to the Executive Summary about combination medication and behavioral treatment studies.
TEP Reviewer #4	General Comments	The authors may wish to reconsider whether the combined use of drugs with behavioral/parent training should be covered in the section on antipsychotics (where it sits currently), or in the section on adjunctive treatments, or whether it merits its own section. I suggest that it does not belong in the current section on antipsychotics, since these studies do not reflect on the use of medication alone, unlike all the other studies that are described in that section. A stand-alone section on combined approaches might be most appropriate.	We created a new section within the Results section of the report to highlight those studies that evaluated combination approaches.

TEP Reviewer #5	General Comments	The medical report is nicely contextualized and clinically meaningful. The key questions are clearly stated and well-formulated.	Thank you for your comments.
TEP Reviewer #5	General Comments	One issue for the medical report that should be addressed early and elaborated upon is that the minimum sample size changed between the original systematic review and the current review (from 30 to 10 subjects). This is a substantial change and could mean that smaller studies prior to 2010 were never captured; whereas smaller studies were captured after 2010. I don't think the authors need to go back and capture the earlier literature, but it at least merits discussion as an important weakness.	The medical review does include those earlier studies with a smaller sample size that would not have been addressed in the 2011 review; however, we note as a limitation that we may have missed some earlier studies as we did not complete a de novo search for such studies but used information about studies excluded in the 2011 review to identify such studies.
TEP Reviewer #1	Introduction	The introduction is quite clear in terms of definition of autism spectrum disorder (ASD). The first paragraph summarizes goals of treatment and complication of treatment (and outcome) by comorbid conditions. The third paragraph of the introduction (2nd paragraph of treatment) would benefit from an introductory/ summary sentence to more clearly specify that some medications have approval by FDA for treatment of comorbid conditions (NOT core symptoms) and most are off label.	We have added text to clarify this statement to the Introduction.
TEP Reviewer #1	Introduction	The last sentence in the intro (under treatment) might be clarified that there are other treatments (not just “devices”) that might be used to address comorbid conditions (e.g., supplements).	We have added text to clarify this statement to the Introduction.
TEP Reviewer #2	Introduction	Succinct. Issues in treatment identified (no consensus, need for evidence base, individualized approaches to intervention)	Thank you for your comments.
TEP Reviewer #3	Introduction	The introduction is concise, well written and well referenced. for both the medical therapies and the sensory therapies the writing is focused on these therapies; there is not a need for extensive discussion of ASD as this report is of interest to professionals with experience with ASD.	Thank you for your comments.
Public Reviewer #2 (Tristram Smith)	Introduction	Well written and concise	Thank you for your comments.
TEP Reviewer #4	Introduction	p. 119, line 33/34 - please review the grammar of this sentence.	Revised, thanks for noting this.
Peer Reviewer #1	Introduction	This provides a clear rationale for the review. There is a short but concise description of ASD and the problems associated with the condition. The need for a review of medical interventions is well justified.	Thank you for your comments.
Peer Reviewer #1	Introduction	The key issues studied (impact on core autism symptoms and behavior problems, risk of harm, long-term effects, modifiers of treatment, generalization to other contexts etc.) are all highly relevant to the treatment of young children with ASD. The the range of outcome variables studied is also extensive and comprehensive.	Thank you for your comments.

TEP Reviewer #5	Introduction	The medical introduction is well-written and appropriate. I would consider including "cognitive or language impairment" as separate from ASD criteria, however, since this is a key distinction in the DSM5.	We have revised text in the Introduction to note language impairments as well.
TEP Reviewer #1	Methods	Inclusion and exclusion criteria are well described and justifiable. For the medical report, for consumers who did not read the 2011 report, the authors might want to reiterate the justification for age range of children with ASD (2-12 years).	We have added information on our rationale for this focus to the Scope of Review section.
TEP Reviewer #1	Methods	The analytic framework explicitly stated, including model used (PICOTS) and where KQ fit in. Literature search strategy robust and well described.	Thank you for your comments.
TEP Reviewer #1	Methods	The definitions of outcome measures described risk of bias assessment of individual studies and strength of the body of evidence.	Thank you for your comments.
Peer Reviewer #2	Methods	Both reviews/Search Strategy: Why were SCI and SSCI (ISI Web of Science) not searched?	We chose not to search the Web of Science database given its significant overlap with MEDLINE and PsycInfo, both of which we searched for the review.
Peer Reviewer #2	Methods	Both reviews/Gray Literature: Was the ISRCTN register searched? This is the other major database in addition to Clinical Trials.gov. The report only speaks of ”other” registries.	We searched the ISRCTN and have noted this explicitly in the report.
Peer Reviewer #2	Methods	Both reviews: Were systematic reviews searched for additional RCTs? This might have been important, see below.	We did search the reference lists of recent systematic reviews. We added the study noted below while the report was undergoing peer review.
TEP Reviewer #3	Methods	Inclusion / exclusion criteria are justifiable. Key questions are pertinent and guided clinically relevant issues. Diagnostic criteria are satisfactory, given that criteria changed during the period studied but most likely had little effect on any published studies during this period. Statistical methods are appropriate.	Thank you for your comments.
Public Reviewer #2 (Tristram Smith)	Methods	Appropriate key driver questions and appropriate framework for the analysis.	Thank you for your comments.
Public Reviewer #2 (Tristram Smith)	Methods	Well written and clear	Thank you for your comments.
TEP Reviewer #4	Methods	Almost all of the studies reviewed are noted to have "small" sample size, but the criteria for this judgment are not provided (or, I didn't find it). What constitutes small? medium? large? Similarly, what is the justification for using cut-offs of 10 and 20 for sample size (understanding the need for larger # in the non-RCT, but why specifically 10 and 20)?	We did not set specific parameters for small, medium, or large; we acknowledge that our description of "small" reflects a largely arbitrary judgement, but given that studies in ASD have included more than 100 participants, we feel that it is appropriate to consider most studies in the reviews as "small." Moreover, most studies noted as a limitation their small sample size.

			We set the sample size criteria of 10 for RCTs and 20 for other types of studies in consultation with a panel of technical experts. Interventions to address ASD are frequently behavioral in nature and highly intensive. They are also frequently adapted to be targeted to specific study participants given the significant heterogeneity of individuals with ASD. In part because this makes ASD research quite complex and intensive, study sizes tend to be small. A cutoff sample size of 20 provides a balance, allowing us to review and comment on adequate literature for the review but with studies large enough to suggest effects of the interventions. We selected a minimum sample size of 10 for RCTs because we felt that the typically greater controls for bias and rigor helped to mitigate limitations of a smaller sample size.
TEP Reviewer #4	Methods	p.36, line 38/39 - Please review the grammar of this sentence.	We revised this text to clarify.
TEP Reviewer #4	Methods	p. 129 - Figure 2 - A very large number of studies were excluded because they did not address a KQ. It would be helpful to understand what these studies did address. Without that explanation, readers may be skeptical about the exclusion of such a large corpus.	We note that the appendix includes a list of studies with exclusion reasons, which are presented by broad category such as relevance to a key question or ineligible age range. Because the current reviews focused only on medical or sensory-focused treatments, studies that addressed another type of intervention would be excluded, as would basic science and non-intervention studies.
Peer Reviewer #1	Methods	Inclusion and exclusion criteria are clearly stated and appropriate. Focusing only on children between the ages of 2-12 seems particularly important given our lack of understanding of the possible risks or advantages of using long-term medications in this age group.	Thank you for your comments.
Peer Reviewer #1	Methods	Search strategies are explicitly stated, relevant and logical. The need for an extension to the previous 2011 review is also well justified.	Thank you for your comments.
Peer Reviewer #1	Methods	The definitions/diagnostic criteria used are appropriate and the choice of outcome measures is fitting. The statistical methods used are also appropriate and well explained.	Thank you for your comments.
Public Reviewer #2 (Tristram Smith)	Methods	The Methods are generally appropriate. However, it is important to note that guanfacine isn't a stimulant; it's an a2-adrenoceptor agonist.	We have revised the grouping of these studies.
TEP Reviewer #5	Methods	In the medical report, the authors note that they did not complete a meta-analysis for risperidone because only three studies qualified. I am puzzled by this because five active treated populations seem	As noted in the report, we attempted to perform a quantitative meta-analysis for the effects of risperidone on ABC subscale outcomes but the

		to qualify by my count (two from the fixed dose study from Kent et al).	small number of studies limited the analysis. We did not count the low and high dose populations in the Kent study as separate populations in our analysis.
TEP Reviewer #5	Methods	I would note somewhere that the CYBOCS-PDD is the same scale as the CYBOCS-ASD.	We revised the report to use the CYBOCS acronym consistently for this scale.
TEP Reviewer #5	Methods	There are some recent studies missing from the report, including a study of atomoxetine (Handen et al) that was recently published and a study of metformin (Anagnostou et al) that was recently published.	We have added the atomoxetine study. The Anagnostou study included children whose mean age was over age 12; thus, it did not meet criteria for the review.
TEP Reviewer #5	Methods	I wonder if the gray literature includes data from the large memantine randomized withdrawal study that has been presented at scientific meetings but not published. (It was negative but the largest RCT in ASD to date.)	We did not search for conference proceedings for the current review, but the study referenced may be Aman et al. 2016 (PMID: 26978327), which is included in the review.
TEP Reviewer #5	Methods	I do not understand how a study where the investigators only report a posthoc analysis of the two treatment intensity groups lumped together (based upon no difference between the two) could be anything other than high risk of bias. This sort of posthoc statistical approach seems to define bias, unless there was an a priori plan to first compare the two active groups and, following some threshold criterion, then lump them if there was no significant difference, but applying an appropriate statistical correction for having done this.	We are unclear which study is being referenced but assume it may be a secondary analysis of data collected in a larger RCT; one study of aripiprazole and one of MPH included in the review present analyses like this. In cases like this, we rate the risk of bias based on the primary paper.
TEP Reviewer #1	Results	Results of literature searches for key questions well described in Results section and illustrated in Figure 2 (flow diagram). Description of included studies well done; table 2 provides a good overview of types of studies included (meeting criteria to address some or all key questions).	Thank you for your comments.
TEP Reviewer #1	Results	KQ1 - good summary of findings and analysis.	Thank you for your comments.
TEP Reviewer #1	Results	All figures, tables and appendices adequate and descriptive.	Thank you for your comments.
TEP Reviewer #1	Results	Reviewer did not identify any missing studies or ones that should have been excluded.	Thank you for your comments.
TEP Reviewer #2	Results	the authors very specifically stated what they set out to review and did exactly what they said they would do. they complemented their review with other published reviews that used other methodologies (eg. Cochrane)and discussed why the results of those reviews might differ from the AHRQ.	Thank you for your comments.
TEP Reviewer #3	Results	The manuscript / report overall is well written and provides an excellent summary of a large number of studies. The breakdown that follows the executive summary provides ample detail; the figures, tables and appendices are quite adequate. I was not able to identify any studies that had been overlooked for either the medical or the sensory therapies reviews.	Thank you for your comments.

Public Reviewer #2 (Tristram Smith)	Results	Good synopsis of the results	Thank you for your comments.
Peer Reviewer #1	Results	I think the authors should be congratulated for their success in summarising very complex and detailed findings in a concise and readable way. The information in the tables is clearly presented and the characteristics of the studies succinctly described. The key message (that evidence for medical interventions is very poor and that the risk of harm is considerable) is clearly highlighted. All figures & tables etc. are appropriate and provide sufficient detail, without being overlong or complex.	Thank you for your comments.
Peer Reviewer #1	Results	Medical interventions are not my main area of expertise, but I could not identify any included studies that should have been omitted, nor spot any obvious studies that should have been included.	Thank you for your comments.
Peer Reviewer #2	Results	Medical interventions/"Studies Comparing Risperidone Plus Parent Training" (p. 21): This heading may be misleading because risperidone was given to participants in both arms. The study seems to have examined the effects of parent training, not of risperidone. Thus, it does not meet inclusion criteria for this review.	We agree and have removed discussion of this study. Because it one of the few studies to examine a combined medical and behavioral treatment, we note that it is fully described in our 2011 review.
Public Reviewer #2 (Tristram Smith)	Results	The Results are generally well-presented, but there are a couple of minor issues: Handen et al. (2015, JAACAP, N = 128) on atomoxetine and parent training appears to have been published within the time period covered by the review. Risperidone adjuncts (ES-16) that have been studied include parent training (Aman et al., 2009, JAACAP, N = 124).	Thank you for pointing out these studies. We have included the Handen study in the updated report and have adapted our discussion of studies that include a medical and behavioral component to place them in a separate section.
TEP Reviewer #4	Results	p.42, last sentence. This sentence, alone, is gratuitous and uninformative. What does it imply that studies were funded by drug manufacturers? Most commonly, this is a suggestion of bias. Are there, in fact, issues of bias that are not already accounted for in the formal review of "risk of bias"? Manufacturer-funded studies also tend to have larger sample sizes than many academic studies. Again, this is, or should be, accounted for elsewhere in the report and its methodology. If it is felt important to provide this information on study sponsorship, I suggest adding information on the sponsorship of all the studies.	We have moved information about industry funding to the overview of studies section of the Results.
TEP Reviewer #4	Results	p. 48, line 14: typo: "...plus am..."	Deleted, thank you.
TEP Reviewer #4	Results	p.133, line 23: "comparatively" should be "comparably"?	Corrected, thanks.
TEP Reviewer #5	Results	In the medical report, guanfacine is inappropriately lumped with stimulants. It is not a stimulant. I would suggest lumping all "ADHD medications" together in a category that includes methylphenidate, guanfacine, and atomoxetine since they all address the same symptoms and are typically considered within the same decision-	We have revised the report to reflect this organization.

		tree.	
TEP Reviewer #5	Results	In the medical report, even though it is published in the literature, I do not think it is appropriate to compare the risperidone + parent training groups to the earlier (separate study) placebo groups in the text of this systematic review. I would drop those (invalid) comparisons.	We have revised our discussion of this study. Two newly published studies do include data from both the RUPP risperidone trial and the RUPP parent training plus risperidone trial. The studies do not combine children from these studies, as was noted in the review.
TEP Reviewer #5	Results	I find it shocking that the authors do not view as significant the observation that 1/3 of children in the HBOT group experienced "middle ear barotrauma." Maybe they have not experienced ear pain, but I would certainly not describe this as an unimportant AE.	We note the high percentage of ear pain (which did not lead to study withdrawal) in one study. We have revised our discussion of harms of HBOT to note this consideration.
TEP Reviewer #5	Results	In the section on "other" treatments, I would suggest maintaining the same format throughout to indicate that only one trial was conducted of buspirone, pentoxifylline, and piracetam.	We were not able to identify a spot in which these studies were not indicated as single studies; however, we have attempted to clarify the presentation of results throughout.
TEP Reviewer #5	Results	I am not sure from the description why N-acetylcysteine is not low SOE.	We considered the SOE to be low for a lack of effect of N-Acetylcysteine on social skills and could not assess SOE for other outcomes given inconsistent findings in 2 studies evaluating this agent.
TEP Reviewer #5	Results	I am not sure from the description why melatonin is not low SOE.	Only 2 studies addressed melatonin and one compared melatonin plus CBT; thus, we did not combine these studies to consider SOE.
TEP Reviewer #5	Results	I am not sure why methylphenidate is low SOE rather than insufficient for oppositional behavior since the data seem inconsistent from their description.	We agree that studies were inconsistent and have changed this rating.
Public Reviewer #2 (Tristram Smith)	Results	Evidence tables appear to be missing in the presentation of findings on "Studies of Nutritional Supplements or Specialized Diets", "Studies of Risperidone Adjuncts", and "Studies of Other Medical Interventions."	We note that we included tables in the medical report text only in those sections for which we could make strength of evidence assessments. All other tables are reported in Appendix F. We have clarified this in the Organization of the Report section.
TEP Reviewer #1	Discussion/Conclusion	The major findings were clearly stated. For both reports, the first paragraphs of the discussion were an excellent summary and clearly stated. Good discussion of benefits.	Thank you for your comments.
TEP Reviewer #1	Discussion/Conclusion	In both reports the future research section addressed gaps and areas for future research quite well.	Thank you for your comments.
Peer Reviewer #2	Discussion/Conclusion	Both reviews/Limitations of the Comparative Effectiveness Review Process (p. 70 of medical; p. 31 of sensory; also in Executive Summary): Whether the high percentage (99%) of ineligible items among non-English abstracts really is unlikely to introduce bias, depends perhaps also on the total number of non-English abstracts, which isn't reported.	We scanned a random sample of non-English abstracts (n=150) and identified few eligible items. We agree that a scan of the entire non-English corpus may have identified more items. We have revised this text to clarify.
Peer Reviewer #2	Discussion/Conclusion	Finally, ref. 42 is not correct – it is to an RCT protocol by the same author, not to the Cochrane review.	We have corrected the references.

Public Reviewer #2 (Tristram Smith)	Discussion/Conclusion	Concise and good detailing of limitations	Thank you for your comments.
Public Reviewer #2 (Tristram Smith)	Discussion/Conclusion	The Discussion is generally consistent with the findings of this review and is likely to be helpful to providers and families. I think it would be important to insert one additional point in "Research Gaps": Commentators have long questioned the theoretical underpinnings and proposed mechanisms of action for sensory-based interventions, especially sensory integration and sensory diets (e.g., Arendt et al., 1988, AJMR). Some have proposed more parsimonious explanations of effects if present such as reinforcing or relaxing properties of the activities and attention from therapists (e.g., Lang et al., 2012, RASD).	Thank you for your comments. We have expanded our discussion of the need to understand sensory mechanisms better.
Peer Reviewer #1	Discussion/Conclusion	The authors' conclusions are clearly stated. However, it seems to me, given the lack of clear evidence that medical treatments have any significant impact on reducing core autism symptoms or improving behavioural problems, together with the risk of harm, that the conclusions should be stronger. Thus, although the authors conclude that "This review provides some evidence for decision making about medical interventions for children with ASD", in fact, most medications appear to have few positive effects, even in the short term, and there is almost no evidence of longer term outcomes. These findings more or less repeat those of their earlier (2011) review. Thus, and despite the authors' conclusion that methodology has improved somewhat in the interim, there is no additional positive evidence to support the use of these treatments. The use of nutritional supplements/diets etc. receives even less support. Hence, the authors conclude that "the literature base is currently insufficient to inform our understanding of the time to effect of interventions, longer term effectiveness of interventions, generalizability of effects outside the treatment context, effectiveness and applicability to broader ASD populations, and components that may drive effectiveness" Given these caveats, and the fact that the situation has changed little since their last review I would suggest the time has come to conclude that, until appropriately conducted intervention trials are conducted, medical interventions should not be used to treat core autism symptoms or behavioural problems other than in exceptional circumstances. Simply referring to "decisional dilemmas" seems too weak a conclusion and I would suggest that the implications of their major findings, although perhaps unpalatable to some, should be more strongly stated.	We feel that the report's conclusions adequately convey the paucity of evidence for medical treatments.
Peer Reviewer #1	Discussion/Conclusion	The limitations of the review and of the studies it includes are adequately summarized. As far as I was aware, no important literature was omitted form the Discussion. The "future research"	Thank you for your comments.

		section clearly summarises how research in this area needs to be improved.	
TEP Reviewer #1	Discussion/Conclusion	For Medical report: Unfortunately (for the state of research in treatments), KQ1 was the best able to be addressed, and other KQ's could not) (see ES-22). The authors clearly described limitations of the CER and evidence based.	Thank you for your comments. We have attempted to expand our discussion of limitations to be comprehensive.
TEP Reviewer #3	Discussion/Conclusion	The findings for medical interventions are clearly presented, limitations described and recommended future research clearly stated. However, some of the recommendations are unlikely to be reached for practical reasons. For example, there is criticism of the few long-term studies of medications because they are open label with no control arm. unfortunately, it is extremely difficult to keep subjects in placebo arms for 6 - 12 months when they are not perceiving benefit. The tone of the recommendations should not be too negative if there is little hope that some of these studies to resolve questions or strengthen evidence are unlikely to ever be conducted.	We have added text to the Research Gaps section to acknowledge the difficulty of retaining participants and planning longer-term trials.
TEP Reviewer #5	Discussion/Conclusion	In the medical report, I'm not sure that the argument about heterogeneity limiting generalizability is articulated properly. Are they arguing that studies can never be generalizable to the individual child with ASD? Or are they arguing that specific studies with narrower populations are not generalizable? It seems to me that a heterogeneous study population is likely most similar to the general ASD population.	We have attempted to clarify this section to note that the heterogeneity of study populations parallels the heterogeneity of children with ASD and that treatment decisions must be individualized.
Public Reviewer #2 (Tristram Smith)	References	Appropriate and up to date	Thank you for your comments.